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# SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SOME OXISURAN METABOLITES AND THEIR O-METHYLDERIVATIVES

J.L. GARCIA RUANO*, C. PEDREGAL and J.H. RODRIGUEZ

Departamento de Química (C-I) Universidad Autónoma de Madrid
Cantoblanco 28049-Madrid, Spain

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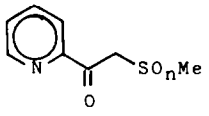
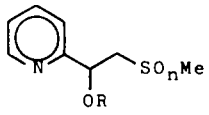
Abstract- The synthesis is given of oxisuran (methylsulphinyl methyl-2-pyridyl ketone)and its metabolites and derivatives, whose structures are 2-Py-CO-$CH_2$-$SO_xCH_3$(X=0, 1, 2) and 2-Py-CHOR-$CH_2$-$SO_nCH_3$(R=H, Me; n=0, 1, 2). From the results obtained in the reaction of oxisuran with different reducing agents, a new stereochemical pathway is suggested to explain the stereoselectivity observed in the reduction of β-keto-sulphoxides with DIBAL. The conformational analysis of hydroxy and methoxyderivatives is discussed in relation with that previously reported for 2-thioderivatives of 1-phenylethanol and their O-methylderivatives. The configurational assignment of diastereoisomeric sulphoxides is made on the basis of their different conformational behaviour, confirming the assignment deduced from the stereoselectivity observed in the reduction of oxisuran.

## INTRODUCTION

Oxisuran (methylsulphinylmethyl-2-pyridyl ketone), is a immunosuppressive agent which has been reported to have the unique property of inhibiting cell-mediated immunity without any concomitant suppression of humoral antibody formation[1]. This property, combined with its low toxicity, makes the compound an interesting candidate for inhibiting the rejection of organ and tissue transplants[2]. Among oxisuran metabolites[3,4], there are the diastereoisomeric alcohols **2α** and **2β**, the sulphone **III** and its respective alcohol **3** and the thioethers I and **1** (Scheme 1).




n = 0(**I**),1(**II**),2(**III**)




| R | n = 0 | 1 | 2 |
|---|---|---|---|
| H | **1** | **2α, 2β** | **3** |
| Me | **4** | **5α, 5β** | **6** |

Scheme 1

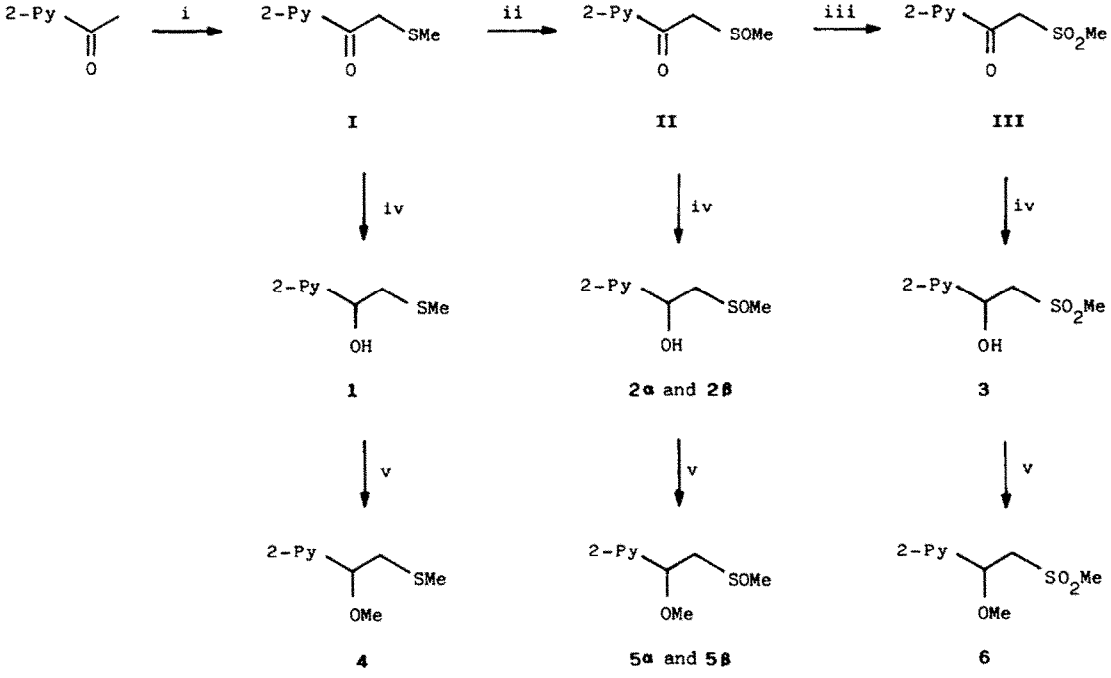
Despite the interest of these drugs little is understood of their action mechanism, and of drug-receptor interactions. Moreover, the configurational assignment of the hydroxysulphoxides **2α** and **2β**, which also show immunosuppressive activity[3], has not been established. In order to clarify some of these questions, we decided to study the relationship between the conformational behaviour of oxisuran and its metabolites and their associated pharmacological properties.This paper, as a first stage of this work, deals with the synthesis of compounds shown in scheme 1, the

configurational assignment of the sulphoxides **2α** and **2β** and the configurational behaviour of the hydroxylated metabolites in different solvents. The O-methyl-derivatives were prepared and studied in order to solve some questions concerning conformational analysis of hydroxyderivatives. The conformational studies of the β-ketothioderivatives and the pharmacological tests will be undertaken in later works.

## RESULTS AND DISCUSSION

A) SYNTHESIS:

The synthetic pathways used in the preparation of compounds from scheme 1 are shown in scheme 2.




i : 1.HBr 2.$Br_2$/AcOH 3.NaSMe. ii : $NaIO_4$. iii : MCPBA(exc) or $NaIO_4$. iv : $NaBH_4$.
v : NaOH/$Me_2SO_4$/TBAI.

Scheme 2

To our knowledge, the only methods found in the literature dealing with the synthesis of oxisuran are patents[5-7]. All of them involve condensation of ethyl 2-pyridyl carboxylate and the methylsulphinyl carbanion generated by the reaction of dry DMSO with NaH. Nevertheless, the moderate yield of this reaction ( 60% in the best case) and the difficulty in reproducing it induced us to develop another more satisfactory method taking 2-acetylpyridine as starting material. The hydrobromide of this compound undergoes monobromination on the methyl group with $Br_2$/AcOH (poor yields were obtained from direct bromination of the pyridylderivative). Subsequent treatment of the bromoderivative with sodium methylthiolate afforded the ketothioether I, whose controlled oxidation allows us to obtain oxisuran II. In spite of the greater number of steps implied, in relation to the previously reported method, an overall yield of oxisuran ranging between 85 and 90 percent is obtained. All individual-step yields are reproducible following the methods indicated in the experimental section. The oxidation of II with an excess of oxidative reagent such as $NaIO_4$ or MCPBA produces ketosulphone III. The reductions of the ketothioderivatives I, II and III with $NaBH_4$ yielded the corresponding

alcohols **1-3**. Independent methylation of these in phase-transfer conditions afforded the corresponding β-methoxythioderivatives **4-6**.

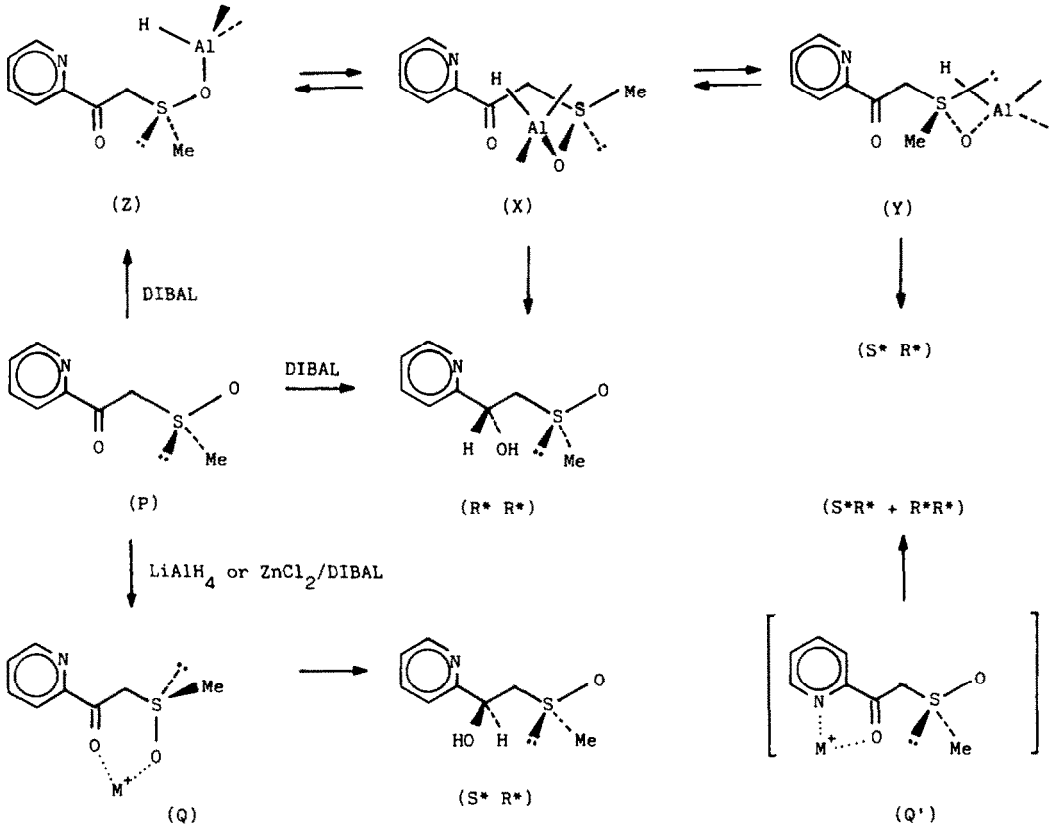
The reduction of the carbonyl group of oxisuran with $NaBH_4$ yielded a mixture of the two diastereoisomeric hydroxysulphoxides **2α** and **2β**, without any observable asymmetric induction. The separation of both epimeric compounds was achieved by fractional crystallization and chromatography. Isomer **2α**(mp 109-110°C) undergoes methylation in phase-transfer conditions, yielding **5α**; in the same way isomer **2β** (mp 75-77°C) yields **5β**. By this procedure we were sure that isomers **α** had identical relative configurations regardless of the oxygenated function. The same could be applied to **β**-epimers.

The immunosuppressive activity, detected for the mixture of hydroxysulphoxides **2α** and **2β**[3], was a further reason to develop methods of stereoselective synthesis of each, as well as to assign their respective relative configurations. Recent papers report the utility of several highly stereoselectives reducing agents of ketosulphoxides. Thus, the reduction of (R)-Ph-CO-$CH_2$-SO-p-Tol(**IV**) with DIBAL/THF yielded a mixture of the corresponding hydroxysulphoxides RR:SR = 18:22 whereas with $LiAlH_4/Et_2O$/THF the stereoselectivity was inverted, affording a mixture RR:SR = 90:10[8]. The presence of $ZnCl_2$ changed the stereochemical results in the reduction with DIBAL, causing them to be identical to those observed with $LiAlH_4$[9], and improving the stereoselectivity[10], which for the present substrate reached a value of RR:SR = 95:5[11]. Moreover, with DIBAL/THF, a mixture RR:SR = 5:95 could be achieved by modifying reaction conditions[11].

With these precedents, we decided to carry out the reduction of oxisuran with the same reducing agents. The reaction with DIBAL in THF at -78°C was unsuccessful, probably due to the low solubility of oxisuran in this solvent, specially at low temperatures. However, the reduction was achieved in $CH_2Cl_2$, yielding a mixture of the hydroxysulphoxides **2α**:**2β** = 92:8 (from $^1$H-nmr spectra of the crude mixture). Assuming the mechanism of action of DIBAL proposed by other authors[11], it was possible to assign the configuration R*R*(or RR,SS) to the major stereoisomer, **2α**. This diastereoisomer would arise from hydride entering the side where the sulphoxide lone pair is located in the presumably preferred conformation of the oxisuran (P in scheme 3) which arranges the two oxygens as distantly as possible in order to minimize dipole-dipole repulsion.

Independently of the validity of the configurational assignment, which we will confirm later, the explanation suggested by Solladié[11] to justify the stereoselectivity of this process does not appear satisfactory, taking into account the results obtained when using $NaBH_4$ as reducting agent. The diastereoisomeric excess observed in the reduction of oxisuran with DIBAL is ∿84%, whereas with $NaBH_4$ it is ∿0%. This fact cannot be attributed to the different size of the two reagents (which are both considered as small hydrides[12]) nor to changes in the composition of the conformational equilibrium of the substrate with the reaction medium(the stereochemical results obtained with $NaBH_4$ do not change with the solvent compositon of the mixture, THF and ethanol). We think that the electrophilic character of DIBAL must be responsible for the observed differences in behaviour, enabling the association of the aluminium with the nucleophilic sulphinylic oxygen before attacking (this association is not possible with $NaBH_4$). The three conformations of the associated oxisuran (X, Y and Z) are depicted in scheme 3. From a steric point of view, rotamer X must be more stable than Y, whereas Z is a non reactive conformation. Therefore, the obtention of the hydroxysulphoxide (R*R*) as major product can also be explained.The stereochemical results obtained by Solladié can also be justified from this approach. New experiences and the election of more adequate models, will permit us to confirm this hypothesis.

The inversion of the stereoselectivity found when $LiAlH_4$ or $ZnCl_2$/DIBAL were used as reducing agents had been explained assuming that, in the presence of $Li^+$ or $Zn^{2+}$, the β-ketosulphoxide is expected to adopt the chelated conformation Q (Scheme 3)determining the hydride attack from the opposing carbonyl face to that




Scheme 3

in the preceeding case. As a consequence, a predominance of diastereoisomer S*R* (or RS,SR) must be expected, in our case compound **2β**. The reduction of oxisuran with $LiAlH_4$ in THF afforded a mixture **2α**:**2β** = 40:60, contrasting this low stereoselectivity with that observed from **IV** (see above). This difference can be explained taking into account two facts: the different size of the groups bonded to sulphur, responsable for the differentiation of the carbonyl faces (larger in **IV** (p-tolyl) than in **II** (methyl)) and the competition between the pyridinic nitrogen and the sulphinylic oxygen in the chelation of $Li^+$ (reduction of the chelating species involving nitrogen,Q', must not be stereoselective). The reaction of oxisuran with the system DIBAL/$ZnCl_2$, must be done in $CH_2Cl_2$(in THF oxisuran is not soluble). In these conditions, a 75:25 mixture of **2α**:**2β** is obtained indicating that the stereoselectivity observed with DIBAL has slightly decrease in the presence of $ZnCl_2$. This results can be rationalized taking into account the low solubility of the $ZnCl_2$ in $CH_2Cl_2$, which determines that only a few molecules of oxisuran are chelated before the attack of DIBAL.

B) CONFORMATIONAL ANALYSIS

The $^1$H-nmr parameters of compounds **1-6**, significant in their conformational analysis, are collected in table 1. The remaining parameters can be found in the experimental section. Compounds **2α** and **2β** have been studied in $CDCl_3$ at lower concentrations than 1 percent (up to c = 0.001%). Nevertheless, in these conditions, the parameters of **2β** remain unaltered with respect to those indicated in table 1

whereas **2α** exhibits deceptively simple spectrum, the only remarkable values being those of $J_{1,OH}$ = 5.3 Hz and δ (OH) = 4.82 ppm obtained when c = 0.001%. The spectra of **4** were recorded in $C_6D_6$ (in $CDCl_3$ deceptively simple spectra were observed) and in a mixture 9:1 of $C_6D_6$: DMSO-$d_6$, tending to deceptiveness when the proportion of DMSO-$d_6$ in the mixture was increased. In addition, the **2α** and **2β** spectra have also been recorded in mixtures of variable composition of $CDCl_3$ and DMSO-$d_6$. The parameters obtained are intermediate between those corresponding to each solvent separately. This fact has allowed us to confirm the assignment of protons H(2) and H(3) (figure 1) in both solvents as is shown in Table 1, suggesting there is not any relevant variation in the conformational preference on changing the solvent.

Table 1. $^1$H-nmr parameters and conformational populations of compounds **1-6***.

| | S[a] | conc. % w/v | Chemical Shifts (ppm) H(1) | H(2) | H(3) | OH | Coup. Const. (Hz) $J_{1,2}$ | $J_{1,3}$ | $J_{1,OH}$ | Populations $x_A$ | $x_B$ | $x_C$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | A | 10 | 4.90 | 2.83 | 3.01 | 4.32 | 7.7 | 4.5 | | 55 | 21 | 24 |
| | A | 0.01 | 4.89 | 2.83 | 3.01 | 4.07 | 7.7 | 4.1 | 4.6 | 56(73) | 16(14) | 28(13) |
| | B | 1 | 4.75 | 2.75 | 2.91 | 5.64 | 7.3 | 4.7 | 5.3 | 51(48) | 22(32) | 27(20) |
| | C | 1 | 4.74 | 2.72 | 2.78 | - | 7.2 | 5.3 | - | 48 | 29 | 22 |
| **2α** | A | 10 | 5.36 | 3.13 | 3.23 | 5.71 | 10.2 | 2.4 | 4.2 | 88 | 0 | 12 |
| | A | 1 | 5.41 | 3.14 | 3.16 | 5.06 | 9.8 | 2.4 | 4.2 | 84(86) | 2(2) | 18(12) |
| | B | 1[b] | 4.97 | 3.00 | 3.08 | 6.06 | 11.1 | 2.4 | 5.5 | 97(93) | 1(7) | 2(0) |
| | C | 10[c] | 4.93 | 3.00 | 3.00 | - | 10.4 | 3.1 | - | 88 | 9 | 4 |
| **2β** | A | 10 | 5.37 | 3.11 | 3.36 | 4.93 | 8.6 | 3.5 | - | 69 | 10 | 22 |
| | A | 1 | 5.43 | 3.07 | 3.36 | 4.83 | 8.8 | 3.0 | - | 72(81) | 4(6) | 24(13) |
| | B | 1 | 5.04 | 3.09 | 3.29 | 5.93 | 7.6 | 5.0 | 5.4 | 54(54) | 27(33) | 19(13) |
| | C | 1 | 5.04 | 3.17 | 3.20 | - | 7.1 | 5.6 | - | 47 | 33 | 20 |
| **3** | A | 0.5[e,f] | 5.35 | 3.36 | 3.41 | 4.72 | 9.8 | 2.0 | 4.2 | 87(92) | 7(-7) | 20(14) |
| | B | 1[d,e,g] | 5.08 | 3.58 | 3.40 | 6.23 | 10.0 | 2.4 | 5.7 | 88(86) | -2(4) | 14(9) |
| | C | 1[e,h] | 5.15 | 3.56 | 3.48 | - | 9.6 | 3.1 | - | 82 | 6 | 12 |
| **4** | D | 2 | 4.61 | 2.92 | 2.96 | - | 7.3 | 4.3 | - | 52(54) | 17(30) | 32(16) |
| | E | 2 | 4.59 | 2.93 | 2.96 | - | 7.3 | 4.4 | - | 52(48) | 18(34) | 31(18) |
| **5α** | A | 1 | 4.82 | 3.19 | 3.08 | - | 10.7 | 2.6 | - | 93(94) | 2(5) | 6(1) |
| | B | 1 | 4.62 | 3.19 | 2.95 | - | 11.0 | 2.6 | - | 96(94) | 2(6) | 2(0) |
| **5β** | D | 1 | 4.90 | 2.93 | 3.07 | - | 7.2 | 5.0 | - | 50(50) | 25(35) | 25(15) |
| | B | 1 | 4.91 | 3.19 | 3.24 | - | 7.6 | 5.0 | - | 54(50) | 27(42) | 19(8) |
| **6** | A | 1[e,g] | 4.91 | 3.63 | 3.29 | | 10.4 | 2.5 | | 92(91) | 1(-3) | 10(12) |
| | B | 1[i,g] | 4.74 | 3.78 | 3.33 | | 9.8 | 2.8 | | 85(86) | 2(4) | 14(10) |

*Values in brackets correspond to the respectives phenylderivatives **7-13** (see text).
[a]Solvent: A $CDCl_3$, B DMSO-$d_6$, C $D_2O$, D $C_6D_6$, E $C_6D_6$/DMSO-$d_6$ (10/1). [b]$J_{3,OH}$ 1.1 Hz. [c]Quasi-Deceptively simple spectrum. [d]$J_{3,OH}$ 0.9 Hz. [e]$J_{2,Me}$ 0.5 Hz. [f]$J_{3,Me}$ 1.0 Hz. [g]$J_{3,Me}$ 1.2 Hz. [h]$J_{3,Me}$ 0.9 Hz. [i]$J_{2,Me}$ 0.3 Hz.

The conformational analysis of 2-Y-1-phenylethanol (Y = SMe, SOMe, $SO_2Me$)[13,14] and their O-methyl derivatives[14,15] have previously been reported in detail. These compounds differ from **1-6** in the nature of their aromatic ring (phenyl instead of 2-pyridyl). Since steric differences between each ring must be negligible, the changes in their conformational behaviours must be attributed to polar interactions between the pyridinic nitrogen (absent in phenylderivatives) and the other heteroatomic functions. As a consequence, the methodology followed in order to establish the conformational behaviour of compounds **1-6** will be similar to that developed in the phenyl series, and so, we remit to references 13-15 to clarify certain

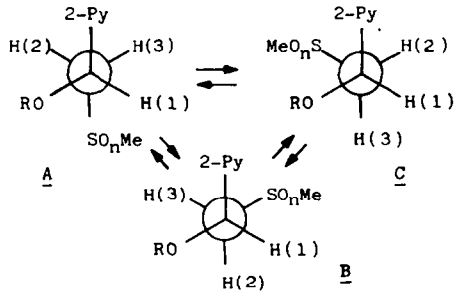



Fig.1. Conformations around the $C_1$-$C_2$ bond.

aspects that we will not repeat here. Therefore, in the present paper, we will merely discuss the differences between those compounds exhibiting the same sulphur functions in each series without commenting on the nature of the interactions common to both.

The conformational populations calculated from the experimental $J_{vic}$ values, taking into account the theoretical ones obtained from Karplus equation parametrized by Altona[16] for trisubstituted ethanes, are summarized in table 1. In spite of the good results that this equation provides in other β-oxygenated thioderivatives[17], the values for these populations have only a semiquantitative validity and therefore should be considered merely as a first approach to discussing the main factors governing conformational equilibria. The corresponding conformational populations for the phenylderivatives **7-13** are also indicated in brackets in table 1.

Compound **1** exhibits a preference for rotamer A hardly modified by dilution or changes in polarity medium. This behaviour constitutes its main difference with respect to the related 2-methylthio-1-phenylethanol (**7**). Compound **7** exhibited a major participation of A owing to the intramolecular association O-H---S which increased with dilution and drastically decreased in DMSO-$d_6$[13]. Therefore, we have to conclude that in substrate **1** the aforementioned association does not exist and steric interactions must be those controlling the conformational equilibrium. However, the value of δ(OH)= 4.07 ppm in solutions $6.10^{-4}$M (≈0.01%) suggests the presence of intramolecular association and, as a consequence, it seems reasonable to assume that pyridinic nitrogen (better acceptor than sulphenylic sulphur) must be the acceptor of such hydrogen bonding. The stereochemistry of the pyridinic ring, favourable for the major effectiveness of the hydrogen bonding (minor distance between O and N) is shown in figure 2. The real situation must be very similar to this since the observed $^3J_{1,OH}$ value (4.6 Hz) implies a dihedral angle of 125.6° between both protons[18], which reveals a slight deviation of planarity depicted in figure 2, relieving the eclipsed C-O and C-N bonds.

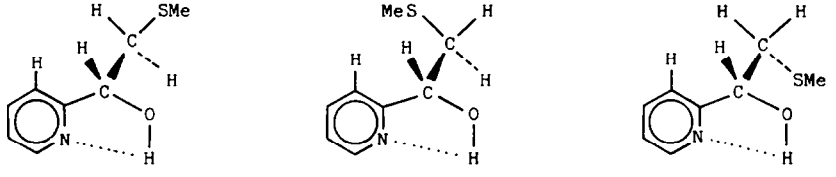
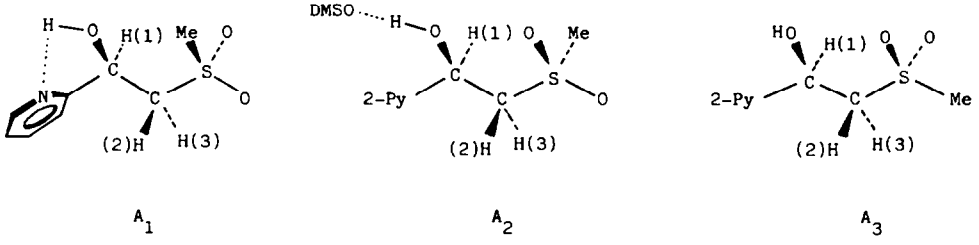



Fig. 2. Staggered rotamers with N---H-O hydrogen bond in compound 1.

Although this hydrogen bonding may be formed in all three conformations, the spatial arrangement of the pyridinic ring determines that its interactions with S-Me grouping are more important in rotamer B ($(C=C/C-S)_{1,3-p}$ interaction) than in C and practically non-existent in A. This ring rigidity contrasts with the free rotation that phenyl group must show in compound **7**; as a consequence, the observed differences in the relative participation of conformers B and C in both compounds may be rationalized. As can be seen from the data of **1** in $D_2O$ and **7** in DMSO the conformational populations are practically identical in both compounds, suggesting that in these polar solvents the only factors that control conformational equilibria populations are the steric ones (almost the same in both compounds) because the corresponding intramolecular associations must be destroyed. The O-methylderivatives **4** and **10**, where hydrogen bondings are not possible, also present a similar participation of rotamers in the equilibrium.

The sulphones **3** and **6** exhibit a pronounced preference for rotamer A, hardly modified by solvent changing.The relative value of $^4J_{2,Me}$ and $^4J_{3,Me}$ constants indicates the preference of $A_1$ with respect to $A_2$ (see figure 3). The reasons for this preference must be the same as those proposed in the case of sulphones **9**[13] and **12**[15] (phenylderivatives), the conformational behaviour of which, respectively identical to **3** and **6**, was controlled by steric effects and attractive electrostatic interactions between oxygenated function and methyl sulphonyl grouping. The scarce contribution of intramolecular hydrogen bonding to the differential stabilization of rotamers of **9** justifies its similarity of behaviour with respect to **3**. In the latter, the high δ(OH) value in diluted solutions of $CDCl_3$ and the $^3J_{1,OH}$ magnitude, compatible with a dihedral angle of 123.5°[18] suggests that the hydroxylic proton must be associated with pyridinic nitrogen adopting a stereochemistry similar to that postulated for the thioether. The absence of $^4J_{3,OH}$ in $CDCl_3$, the observation of which requires a W planar arrangement between the involved protons[19], is in agreement with the required stereochemistry for the association (see $A_1$ in fig. 3). On the other hand,its partial destruction in DMSO-$d_6$ allows the hydroxylic proton, at least partially, to reach the arrangement shown in $A_2$, now enabling observation of the long-range constant with the hydroxylic proton.



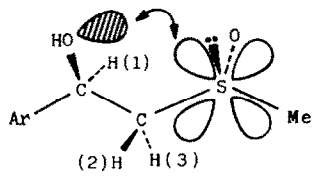

$A_1$ $A_2$ $A_3$

Fig. 3. Conformational equilibrium around the $C_2$-S bond in compound **3**.

In the case of the sulphoxides, the configurational assignment has to be discussed in relation to the conformational behaviour of each diastereoisomer, because of the intimate relationship existing between both of them. As shown in table 1, sulphoxides **2α** and **5α** exhibit a more marked participation of rotamer A than their corresponding epimers **2β** and **5β**. In the hydroxyderivatives, the conformational behaviour observed on changing the solvent from $CDCl_3$ to DMSO-$d_6$ is opposite in both diastereoisomers. Thus, the preference for conformation A in **2α** increases whilst in **2β** is decreased. These differences in the conformational behavior related to the relative configuration of the chiral centres are identical to those observed in the 2-methylsulphinyl-1-phenylethanol (**8α** and **8β**) epimers and in its O-methylderivatives (**11α** and **11β**). The full discussion of this behaviour[14] led us to propose the configuration (RR,SS) for isomer α and (RS,SR) for β. Additionally, these were later confirmed by X-ray diffraction[20]. These assignments, which must also be applied to pyridinic compounds **2** and **5**, are in agreement with those proposed from the reduction mechanism of the ketosulphoxides (see part A).

We will now discuss the differences found between sulphoxides supporting phenyl and pyridyl rings. The presence of a nitrogen atom facilitates the intramolecular association with the OH group. In the case of **2α**, this association hardly differentiates the populations of the rotamers around the $C_1$-$C_2$ bond with regard to those existing in **8α**. The most favoured conformation in both cases (figure 4) arranges the unshared electron pair of the oxygen towards the sulphur atom, which permits a donor-acceptor interaction[14,21]. Since this factor becomes fundamental in the relative stabilization of the rotamers of **8α**[14], the fact that

the O-H---N association has no effect on it justifies a similar conformational behaviour in both substrates. In this sense, there is some experimental evidence that supports the proposed association in **2α**. In DMSO-$d_6$ the long-range coupling constant $^4J_{3,OH}$ was observed in both **2α** and **8α**, presenting similar values (∿1.1 Hz), which indicates a coplanar arrangement equivalent to $A_2$ (fig. 3). However, in $CDCl_3$, this coupling constant remains unaltered in **8α**[14], but disappears in **2α**, suggesting in the latter that the hydroxylic proton adopts a stereochemistry equivalent to $A_1$ (fig. 3) where the coplanarity with H(3) has been lost. From the similar values observed for $^3J_{1,OH}$ in analogous concentrations in **2α** and **3** it may be deduced that the stereochemistry of the hydroxylic proton in both substrates must be identical.




Ar = 2-Py(**2α**), Ph(**8α**)

Fig.4. Donor-acceptor n→d° interaction in A rotamers of compounds **2α** and **8α**

With regard to **2β**, the conformational preferences suggest that the association O-H---N must compete with the other possible O-H---O-S, which was the only one present in **8β**. Taking into account that the sulphinylic oxygen is a better acceptor than both the sulphonylic one and sulphenylic sulphur, it seems reasonable that the aforementioned competition takes place only in sulphoxide **2β**. The existence of a rapid equilibrium between both associated conformations justifies the impossibility of measuring $J_{1,OH}$ (the corresponding signals appear widened but not resolved), whilst in **8β** a clear splitting of the hydroxylic signals ($J_{1,OH}$= 1.9 Hz) appears, which is indicative of the intramolecular association with the sulphinylic oxygen[14]. The indicated competition can justify the differences observed in the conformational populations of **2β** and **8β** in $CDCl_3$, that logically disappear in DSMO-$d_6$ and are not possible in the corresponding methoxyderivative. In the same way, the populations of **1** and **2β** in DMSO-$d_6$ are also very similar in concordance with the little difference in size between SOMe and SMe functions[22] and with the minimization of the electrostatic interactions in this solvent. On the contrary, the differences between **1** and **2α** in both $CDCl_3$ and DMSO-$d_6$ reveal the influence of other interactions, such as the above mentioned donor-acceptor, (only possible in this epimer) which must be scarcely sensitive to changes in the medium polarity.

## EXPERIMENTAL

General: Silica gel used in column chromatography was Merck K-60 (70-230 mesh). Melting points were determined on a Buchi 594392 type S apparatus in open capillary tubes and are uncorrected. Mass spectra (MS) were recorded in a HP-5985 spectrometer in the electron impact (EI) at 70 eV or chemical ionization (CI) (methane as the reagent gas) ionization modes. Mass data are reported in mass unit (m/z) and the values in brackets regard the relative intensity from the base peak (as 100%). IR spectra were obtained on a Pye Unicam SP-1100 spectrometer. Proton NMR spectra were recorded on a Bruker WM-200-SY spectrometer in FT mode. Shifts are reported in ppm down field from internal TMS. In order to observe hydroxyl splitting, the deuterium chloroform was purified by distilling twice from phosphorous pentoxide and anhydrous potassium carbonate. The analyses of the spectra were carried out using the PANIC program on the ASPECT 2000 computer of the spectrometer. We estimate the reliability of all values to be 0.1 Hz and the root mean deviations for the calculated and the experimental lines were usually better than 0.05 Hz.

2-(Bromoacetyl)pyridinium bromide. To a solution of 14.2 g (70 mmol) of 2-acetyl pyridinium bromide in glacial acetic acid, previously heated at 60°C, 4.6 ml (90 mmol) of bromine in bencene were dropwise added. The reaction mixture was cooled at room temperature and the solid was filtered off and washed several times with $CCl_4$. Thus 18.9% of the bromoderivative were obtained. Melts with decomposition at 215°. $\nu_{max}$(KBr) 3100, 1725, 1605, 1520, 785 and 645 $cm^{-1}$. MS(CI): 240 (6.6),

228 (6.8) and 200 (100.0). δ: 4.90 (s, 2H, $CH_2$), 7.44 (m, 1H, $H_5$-Py), 7.72 (m, 1H, $H_4$-Py), 7.99 (m, 1H, $H_3$-Py) and 8.71 (m, 1H, $H_6$-Py).

Methylthiomethyl 2-pyridyl ketone **I**. 2.9 g (41 mmol) of sodium methyl sulphide in 25 ml of anhydrous methanol were slowly added to a solution of 8.9 g (30 mmol) of 2-(bromoacetyl)pyridinium bromide. The mixture was stirred at room temperature, diluted with 50 ml of water and extracted with chloroform. The extracts were dried and concentrated to yield 5.17 g (97.5%) of the ketosulphide **I**, bp 50°/0.1 mm Hg. $\nu_{max}$(film): 3070, 2930, 1695, 1585, 1440, 1290, 1005 and 760 $cm^{-1}$. MS(EI): 167 ($M^+$, 8.5), 152 (19), 134 (21), 121 (26), 106(38), 79 (43), 78 (100), 61 (23) and 51 (90). δ: 2.16 (s, 3H, $CH_3$), 4.02 (m, 2H, $CH_2$), 7.55 (m, 1H, $H_5$-Py), 7.90 (m, 1H, $H_4$-Py), 8.15 (m, 1H, $H_3$-Py) and 8.65 (m, 1H, $H_6$-Py).

Methylsulphinylmethyl 2-pyridyl **II** and methylsulphonylmethyl 2-pyridyl ketones **III**. They were obtained from **I** by oxidation with sodium metaperiodate or m-chloroperbenzoic acid following general methods outlined in the literature[23]. **II**, yield 93% ($NaIO_4$ as oxidant), crystallized from etylacetate, mp 78-79°(lit[4] 80°). $\nu_{max}$ (KBr): 3080, 2900, 1705, 1585, 1440, 1295, 1000 and 620 $cm^{-1}$. MS(CI): 183 ($M^+$, 0.8), 168 (14), 106 (47), 79 (25) and 51 (28). δ: 2.78 (s, 3H, $CH_3$), 4.70 (AB system, 2H, $CH_2$), 7.56 (m, 1H, $H_5$-Py), 7.90 (m, 1H, $H_4$-Py), 8.09 (m, 1H, $H_3$-Py) and 8.73 (m,1H, $H_6$-Py). **III**. Quantitative yield, crystallized from toluene, mp 109-110° (lit[4] 110°). $\nu_{max}$ (KBr): 3040, 2960, 1700, 1585, 1325, 1145, 980 and 785 $cm^{-1}$. MS(CI): 240 $(M+41)^+$ (6), 228 $(M+29)^+$ (5,7) and 200 $(M+1)^+$ (100.0). δ: 3.10 (s, 3H, $CH_3$), 4.97 (s, 2H, $CH_2$), 7.55 (m, 1H, $H_5$-Py), 7.90 (m, 1H, $H_4$-Py), 8.10 (m, 1H, $H_3$-Py) and 8.75 (m, 1H, $H_6$-Py).

**Hydroxythioderivatives**. All were obtained from the corresponding carbonyl parent compounds by reduction with $NaBH_4$ in ethanol by the usual methods[24].

2- Methylthio-1-(2-pyridyl)ethanol **1**. Prepared quantitatively from **I**. bp 99-100°/0.4 mmHg). $\nu_{max}$(film): 3400, 2950, 1595, 1475, 1080 and 765 $cm^{-1}$. MS(EI): 170 $(M+1)^+$ (12), 152 (32), 136 (47), 108 (100), 106 (31), 93 (22), 78 (64) and 51 (24). δ: 2.11 (s, 3H, $CH_3$), 2.98 (m, 2H, $CH_2$), 4.13 (s, 1H, OH), 4.89 (m, 1H, CH), 7.23 (m, 1H, $H_5$-Py), 7.44 (m, 1H, $H_3$-Py), 7.72 (m, 1H, $H_4$-Py) and 8.56 (m, 1H, $H_6$-Py).

2-Methylsulphinyl -1-(2-pyridyl)ethanol **2α and 2β**. They were quantitatively obtained from **II** as an equimolecular mixture. Pure **2α** could be isolated by crystallization from benzene of the reaction mixture, mp 109-110° (lit [4] 112°). $\nu_{max}$(KBr): 3260, 3040, 1595, 1440, 1080 and 785 $cm^{-1}$. MS(CI): 226 $(M+41)^+$ (4.8), 186 $(M+1)^+$(100) and 168 (76). δ:2.73 (s, 3H, $CH_3$), 3.14 (m, 2H, $CH_2$), 5.06 (s, 1H, OH), 5.41 (m, 1H, CH), 7.25 (m, 1H, $H_5$-Py), 7.51 (m, 1H, $H_3$-Py), 7.76 (m, 1H, $H_4$-Py) and 8.55 (m, 1H, $H_6$-Py). The **β** diastereoisomer could be isolated in pure state by column chromatography using ammonium hydroxide (0.92 sp gr) (ethanol/diethyl ether (1:7:12) as eluent. mp 75-77° (lit [4] 74°). $\nu_{max}$ (KBr): 3260, 3040, 1595, 1080, 960 and 630 $cm^{-1}$. MS(CI): 226 $(M+41)^+$ (2.1), 214 $(M+29)^+$ (0.5), 186 $(M+1)^+$ (31.6), 168 (25) and 122 (100). δ: 2.74 (s, 3H, $CH_3$), 3.21 (m, 2H, $CH_2$), 4,83 ( s, 1H, OH), 5.43 (m, 1H, CH), 7.25 (m, 1H, $H_5$-Py), 7.51 (m, 1H, $H_3$-Py), 7.77 (m, 1H, $H_4$-Py) and 8.55 (m, 1H, $H_6$-Py).

2- Methylsulphonyl -1-(2-pyridyl)ethanol **3**. Prepared from **III**. Yield 89%. Crystallizes from chloroform, mp 150-152° (lit [4] 152°). $\nu_{max}$(KBr): 3200, 3070, 1595, 1300, 1140, 785 and 755 $cm^{-1}$. MS(CI): 242 $(M+41)^+$ (25.6), 230 $(M+29)^+$ (39.3) and 202 $(M+1)^+$ (100). δ: 3.13 (s, 3H, $CH_3$), 3.39 (m, 2H, $CH_2$), 4.72 (s, 1H, OH), 5.35 (m, 1H, CH), 7.30 (m, 1H, $H_5$-Py), 7.40 (m, 1H, $H_3$-Py), 7.78 (m, 1H, $H_4$-Py) and 8.58 (m, 1H, $H_6$-Py).

**Methoxythioderivatives**. All of them were prepared by methylation of hydroxy compounds using the phase-transfer system $Me_2SO_4$/NaOH/TBAI reported by Herz[25].

2-[1-Methoxy-2-(methylthio)ethyl]pyridine **4**. Obtained from **1**, yield 87%. It was purified by distillation, bp 70-72°/0.1 mmHg. $\nu_{max}$(film): 3070, 2840, 1590, 1445, 1120 and 760 $cm^{-1}$. MS(EI): 183 $M^+$ (2.1), 168 (2), 152 (31), 136 (100), 122 (62), 93 (23), 78 (21) and 51 (8). δ:2.10 (s, 3H, $SCH_3$), 2.91 (m, 2H, $CH_2$), 3.37 (s, 3H, $OCH_3$), 4.48 (m, 1H, CH), 7.22 (m, 1H, $H_5$-Py), 7.44 (m, 1H, $H_3$-Py), 7.73 (m, 1H, $H_4$-Py) and 8.79 (m, 1H, $H_6$-Py).

2-[1-Methoxy-2-(methylsulphinyl)ethyl]pyridine[7] **5α and 5β**. The diastereomers **5α** and **5β** were prepared independently from the corresponding hydroxysulphoxides **2α** and **2β** respectively. Both epimers were purified by thin-layer chromatography using methanol as eluent **5α**,yield 93%. $\nu_{max}$(film): 3070, 2830, 1590, 1435, 1120 and 765 $cm^{-1}$. MS(CI): 200 $(M+1)^+$(68), 184 (41), 152 (47), 136 (100) and 122(22). δ: 2.65 (s, 3H, $SCH_3$), 3.13 (m, 2H, $CH_2$), 3.39 (s, 3H, $OCH_3$), 4.82 (m, 1H, CH), 7.26 (m, 1H, $H_5$-Py), 7.42 (m,1H, $H_3$-Py), 7.75 (m, 1H, $H_4$-Py) and 8.63 (m, 1H, $H_6$-Py). **5β**, yield 90%. $\nu_{max}$(film): 3080, 2850, 1595, 1475, 1120, 1050 and 765 $cm^{-1}$. MS(CI): 200 $(M+1)^+$ (100), 184 (13.3), 182 (60), 168 (6) and 152 (1). δ: 2.64 (s, 3H,$SCH_3$), 3.17 (m, 2H, $CH_2$), 3.29 (s, 3H, $OCH_3$), 4.74 (m, 1H,CH), 7.19 (m, 1H, $H_5$-Py), 7.38 (m, 1H, $H_3$-Py), 7.69 (m, 1H, $H_4$-Py) and 8.55 (m,1H, $H_6$-Py).

2-(1-Methoxy-2-(methylsulphonyl)ethyl)pyridine **6**. Obtained from **3**. It was purified by column or thin-layer chromatography using ethylacetate as eluent, yield 80%. (Found: C, 50.11; H, 6.21; N, 6.43; S, 14.62. $C_9H_{13}NO_3S$ requires C, 50.21; H, 6.09; N, 6.51; S, 14.89%). $\nu_{max}$(film): 3080, 2850, 1590, 1475, 1320, 1150 and 770 $cm^{-1}$. MS(CI): 256 $(M+41)^+$(5), 244 $(M+29)^+$(7), 216 $(M+1)^+$(100) and 122(10). $\delta$: 3.08 (s,3H, $SCH_3$), 3.38 (s,3H,$OCH_3$), 3.46 (m, 2H,$CH_2$), 4.91 (m, 1H,CH), 7.31 (m, 1H, $H_5$-Py), 7.42 (m, 1H, $H_3$-Py), 7.78 (m, 1H, $H_4$-Py) and 8.68 (m, 1H, $H_6$-Py).

Reduction if **II**. A. Lithium aluminium hydride. A solution of 1 mmol of oxisuran in 10 ml of THF was added to a suspension of 1 mmol of $LiAlH_4$ in 10 ml of THF cooled at -78°C. After 3 h at -78°C, the reaction mixture was decomposed with a aqueous saturated ammonium chloride solution and extracted continuous extraction with $CH_2Cl_2$, yield 90%. The diastereoisomeric excess was determined on the crude product by $^1H$-nmr after the solvent evaporation. B. Diisobutyl aluminium hydride. To a solution of 1 mmol of oxisuran in 10 ml of anhydrous $CH_2Cl_2$ at -78°C, was added 1.1 ml (1.1 mmol) of a 1M solution of DIBAL in hexane. After 1h at -78°C, the reaction mixture was decomposed by adding 10 ml of MeOH at -78°C. The solvent was then evaporated, the residue was diluted with water and extracted continuous extraction with $CH_2Cl_2$. The organic layer was dried and evaporated, yield 100%. C. $ZnCl_2$/DIBAL. To a solution of 1 mmol of oxisuran and 1.2 mmol of $ZnCl_2$ anhydrous in 10 ml of $CH_2Cl_2$ at -78°C was added 1.1 ml (1.1 mmol) of a 1M solution of DIBAL in hexane. After 3 h at -78°C, the reaction mixture was treated as in case B, yield 82%.

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